UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,746	03/03/2004	Franz Paul Armbruster	0756-0124P	2900

2292 7590 02/05/2009

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
HAQ, SHAFIQUL	
ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
02/05/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/790,746	ARMBRUSTER ET AL.	
	Examiner	Art Unit	
	SHAFIQUL HAQ	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-9 and 11-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-9 and 11-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

1. Claims 1-4, 7-9 and 11-13 are pending and are examined on merits.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-4, 7-9 and 11-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 1 recites the term "25-hydroxy vitamin D metabolite" and "1α, 25-hydroxy vitamin D metabolite". The term metabolite at the end of the compound is confusing because it intends to mean metabolite of "25-hydroxy vitamin D" or metabolite of "1α, 25-hydroxy vitamin D". Applicants are suggested to delete "metabolite" to clearly describe that the compounds are "25-hydroxy vitamin D" and "1α, 25-hydroxy vitamin D".

5. Claim 1 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for not clearly reciting the active steps for measuring the amount of 25-hydroxy vitamin D metabolite and 1α, 25-hydroxy vitamin D metabolite or both in a sample. It is recommended to re-write each steps clearly so that each of the reaction steps in the method steps are clearly defined. Further, claim 1 recites "vitamin D derivative displaces a 25-hydroxy- or 1α, 25-hydroxy vitamin D metabolite or both" in lines 4-5 and recites "wherein a displacement efficiency of approximately 1 is obtained by

using a vitamin D derivative of formula (I)" in lines 6-7. It is confusing form the claim language as to "vitamin D derivative of formula (I)" is used at what step in the method and also it is confusing as to whether the "vitamin D derivative" that is recited in line 4 is the "vitamin D derivative of formula (I)" or not.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-3 and 11-13 are again rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for measuring the amount of separated (isolated) 1α, 25-hydroxy vitamin D metabolite, does not reasonably provide enablement for measuring the amount of 1α, 25-hydroxy vitamin D metabolite in a sample in the presence of 25-hydroxy vitamin D metabolite in the sample (i.e. in the presence of both the metabolites in a sample) without the separation (isolation) of 1α, 25-hydroxy vitamin D metabolite from the sample. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The method as claimed measures both 25-hydroxy vitamin D metabolite and 1α, 25-hydroxy vitamin D metabolite in a sample by competitive protein binding assay using a vitamin D derivative of formula (I) as a competitor. However, in a sample where the 1α, 25-hydroxy vitamin D metabolite is very low (e.g. human serum where 25-hydroxy vitamin D metabolite to 1α, 25-hydroxy vitamin

D metabolite is 1000:1; see paragraph 2, page 34 of specification), the displacement of vitamin D derivative of formula (I) from the vitamin D binding protein would be mainly due to 25-hydroxy vitamin D metabolite and thus the displacement cannot be correlated to the amount of 1α, 25-hydroxy vitamin D metabolite in the serum sample. See second paragraph (page 34) of specification and page 7 of Applicants' argument (10/10/07), which describe separation of 1α, 25-hydroxy vitamin D from sample by column chromatography for subsequent detection of 1α, 25-hydroxy vitamin D by competitive protein binding assay and thus the method as claimed is not enabled for measuring 1α, 25-hydroxy vitamin D metabolite in the presence of both 25 hydroxy vitamin D metabolite and 1α, 25-hydroxy vitamin D metabolite in the sample.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-4, 7-8 and 11 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Holick et al. (WO 97/24127).

Holick teaches methods for detecting the presence of vitamin D analogs and their metabolites in a sample using labeled vitamin D compounds (i.e. vitamin D derivative) in the assay method (see field of invention). The vitamin D metabolites includes , 1,25 dihydroxy vitamin D3, 25 hydroxy vitamin D2 etc. (page 1, lines 12-25

and page 5, lines 10-14) The labeled vitamin D derivative of Holick (see compounds B and C of example 2 and 3 of pages 14-15) reads on the compound of the formula of claim 1 when R represents R a 25-hydroxy side-group of vitamin D2 or of vitamin D3, Y=H, A= functional group coupled via a spacer group, which can be bound by a protein with high affinity (see definition of A in lines 9-16 of specification wherein A can be biotin). Holick discloses a method in which labeled vitamin D derivative is first allowed to bind to a protein capable of binding to the vitamin D derivative and which is attached to a solid support. Sample containing vitamin D metabolite is then added to effect displacement of the labeled compound from said protein and Holick discloses that preferred protein is vitamin D binding protein (DBP) (see pages 11-12). Holick discloses different immunoassay methods (page 10, lines 21-25 and page 12, lines 9-11) and solid phase support including dextran, agarose, polystyrene and microtitration plate (page 11, lines 27-29) and the solid phase can be beads, plates or tubes (page 10, lines 15-16).

Holick discloses displacement of vitamin D derivatives from vitamin D binding protein (i.e. competitive detection) but remain silent about displacement efficiency with the vitamin D derivative. However as described above, the labeled vitamin D derivatives of Holick are very similar or the same as the vitamin D derivatives of formula (I) of instant application and they are expected to show similar properties (e.g. similar displacement properties from vitamin D binding proteins). PRODUCT, MPEP §2112 states "[Where] the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or

substantially identical processes, a prima facie case of either anticipation or obviousness has been established." In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)(emphasis added).

With regard to Kit of claims 4 and 7-8, Holick discloses that the labeled compounds are ideally suited for the preparation of a kit and the kit may contain labeled vitamin D derivative, vitamin D binding protein and avidin coated beads, plates etc. (page 10, lines 9-20). Holick does not recite standardized quantity of vitamin D derivatives but standardized quantity of components in a kit composition is obvious to one of ordinary skill in the art.

10. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Holick et al. (WO 97/24127) as described above and further in view of DeLuca et al. (US 5,064,770).

See above teaching for Holick et al.

Holick et al disclose kit comprising solid phase (e.g. beads) and vitamin D derivative but differ from the instant application in failing to disclose magnetic microparticle as solid phase.

DeLuca et al. in a binding assay to determine 1, 25-dihydroxy vitamin D receptor disclose using magnetic particle for anchoring binding molecules to the particle.

Since the use of magnetic particle is very common in the field of immunoassay and magnetic particle has been disclosed for detection of vitamin D binding protein (DeLuca et al.), it would be obvious to one of ordinary skill in the art at the time the invention is made to include magnetic particle in the method of Holick et al. for

detection of vitamin D metabolites involving vitamin D binding protein with a reasonable expectation of success.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-4, 7-8 and 11-13 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,787,660 in view of Holick et al. (WO 97/24127. (Note that the method claims were not restricted out in the parent application i.e. there was not restriction requirement on the method claims in parent application).

Claims 1-5 of US patent discloses 25-OH vitamin D derivatives which reads on the vitamin D derivative of formula (I). See claims 2 and 5, wherein A can be selected from biotin.

The claims of US patent '660 do not teach using the derivatives in competitive immunoassays.

Holick teaches methods for detecting the presence of vitamin D analogs and their metabolites in a sample using labeled vitamin D compounds (i.e. vitamin D derivative) in the assay method (see field of invention). The vitamin D metabolites includes , 1,25 dihydroxy vitamin D3, 25 hydroxy vitamin D2 etc. (page 1, lines 12-25 and page 5, lines 10-14) Holick discloses a method in which labeled vitamin D derivative is first allowed to bind to a protein capable of binding to the vitamin D derivative and which is attached to a solid support. Sample containing vitamin D metabolite is then added to effect displacement of the labeled compound from said protein and Holick discloses that preferred protein is vitamin D binding protein (DBP) (see pages 11-12). Holick discloses different immunoassay methods (page 10, lines 21-25 and page 12, lines 9-11) and solid phase support including dextran, agarose, polystyrene and microtitration plate (page 11, lines 27-29) and the solid phase can be beads, plates or tubes (page 10, lines 15-16).

Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to include the 25-OH derivatives of vitamin D in the competitive immunoassay method of Holick with the expectation of optimization and improving the detection sensitivity of 25-OH vitamin D metabolite and 1,25-dihydroxy vitamin D metabolite in a sample with a reasonable expectation of success.

Holick discloses displacement of vitamin D derivatives from vitamin D binding protein (i.e. competitive detection) but remain silent about displacement efficiency

with the vitamin D derivative. However as described above, the labeled vitamin D derivatives of Holick are very similar or the same as the vitamin D derivatives of formula (I) of instant application and they are expected to show similar properties (e.g. similar displacement properties from vitamin D binding proteins). PRODUCT, MPEP §2112 states "[Where] the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established." In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)(emphasis added).

With regard to Kit of claims 4, 7-9 and 13, Holick discloses that the labeled compounds are ideally suited for the preparation of a kit and the kit may contain labeled vitamin D derivative, vitamin D binding protein and avidin coated beads, plates etc. (page 10, lines 9-20). Holick does not recite standardized quantity of vitamin D derivatives but standardized quantity of components in a kit composition is obvious to one of ordinary skill in the art. With regard to length of biotin group and spacing group, the length of spacers and the length of biotin and spacer of at least one of the compounds A-C and D of the reference encompass the length of 0.9 to 1.5 nm of instant application.

Response to Argument

13. Applicant's arguments and amendments filed 11/26/2008 have been fully considered and are persuasive to overcome some of the rejections under 35 USC 112 second paragraph, but they are not persuasive to overcome the rejections under 35 USC

103 (a). However, a further review of the claims necessitated 112 second paragraph and obviousness-type double patenting rejections which are described in this office action.

With regard to Holick's reference, Applicants argued that the "biotin conjugate" shown on page 17 in Holick '127 is not a biotin. Applicants argued that the intervening chain [between the 'biotin' and the vitamin D metabolite in Figure 6] is a long ester to 25-hydroxy vitamin D moiety. The chemical formula shows an ester and the chemical reaction shown in Figure 6 produces and ester, the ester link of Holick would be subjected to enzyme cleavage (with esterases) since human blood serum an plasma contain esterases. Applicants further argued that Holick '127 merely shows that there was a vitamin D ring system present in its disclosure but there is not proof that 25 OH-group was present in any one of the target compounds of Holick. Applicants further argued all the binding and ELISA studies in Holick '127 were made with derivatives of vitamin D rather than 25 OH-vitamin D and Holick '127 used biotinylated vitamin D instead of biotinylated 25 OH-vitamin D.

Applicants arguments have been fully considered but are not convincing because Holick '127 clearly disclose biotinylated 25-OH vitamin D (see example 3 of page 15 and example 5 of page 17) and clearly disclose "biotin" in the biotin conjugate. See lines 4-5 of page 15, wherein Holick '127 clearly teaches a method for the synthesis of the conjugate and wherein "**biotin**-X-NHS" from Calbiochem Inc. is used in the synthesis process and the conjugate does not have an ester linkage and the conjugates and are the same or very similar to the conjugate of instant claim 1,

when in the formula (I), Y=H. Holick '127 clearly discloses a method in which labeled vitamin D derivative (i.e. 25-OH-D3 biotin conjugate) is used in a competitive immunoassay (page 18, lines 12-14).

Applicants further argued that the present invention has an unexpected and unexplained 1:1 displacement ratio rather than 1:11 displacement ratio, allowing the present invention to be more precise that that of Holick. However, the Examiner maintains that since the labeled vitamin D derivatives of Holick are very similar or the same as the vitamin D derivatives of formula (I) of instant application and they are expected to show similar properties (e.g. similar displacement properties from vitamin D binding proteins). PRODUCT, MPEP §2112 states "[Where] the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established." In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)(emphasis added).

In addition, the instant claims are not limited to specific amounts and, thus, applicant's argument is not persuasive. In summary, based on the teachings of the cited prior art, the utilization of biotinylated 25-OH-vitamin D compounds in assaying for 1,25(OH)2-vitamin D and 25-OH-vitamin D would have been obvious to the skilled artisan in the art at the time of the present application.

With a regard to 112 first paragraph rejection, Applicants arguments are not persuasive because the claim as recited does not require separation of 1α, 25-

hydroxy vitamin D metabolite from the sample or the use of anti-1α, 25-hydroxy vitamin D antibody or a binding protein specific to only 1α, 25-hydroxy vitamin D.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shafiqul Haq whose telephone number is 571-272-6103. The examiner can normally be reached on 7:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shafiqul Haq/
Examiner, Art Unit 1641